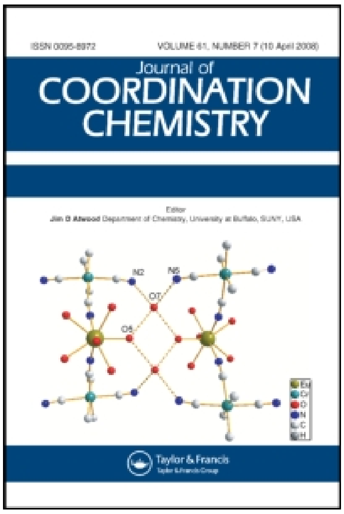

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Synthesis and crystal structure of lithium alendronate

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Synthesis and crystal structure of lithium alendronate

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A new monovalent metal alendronate $[Li(H_4L)(H_2O)_2]$ $[H_5L = H_2N(CH_2)_3C(OH)(PO_3H_2)_2]$ (**1**) has been synthesized from lithium carbonate and alendronic acid and characterized by single-crystal X-ray diffraction as well as infrared spectroscopy, nuclear magnetic resonance, and electrospray mass spectrometry. Compound **1** is monomeric, and the four coordinate Li ion is coordinated by one oxygen of each phosphonate group and two waters in a distorted tetrahedral array. Extensive hydrogen bonding links each complex molecule to 10 others giving a 3-D supramolecular network.

Keywords: Lithium; Alendronate; Crystal structure; Diphosphonate complexes

1. Introduction

The chemistry of metal diphosphonates has been of great interest because of their potential applications which include catalysis, photochemistry, materials chemistry, ion exchange, and intercalation chemistry [1]. Hydroxymethyldiphosphonic acids are extremely good at complexing with various metal ions enabling them to be transported through biological media [2]. Alendronic acid (4-amino-1-hydroxybutylidene-1,1-diphosphonic acid, H_5L) as the sodium salt, NaH_4L, is used in the treatment of bone diseases such as osteoporosis, in both men and women [3]. The presence of the NH_2 group increases the potency of drugs of this type. A few metal complexes of alendronic acid have been crystallographically characterized, including derivatives of Na, Ca, Mn, Co, Zn, and Cd [4–8].

We now describe the synthesis, crystal structure, and spectroscopic characterization of a second Group 1 metal diphosphonate $[Li(H_4L)(H_2O)_2]$ (**1**) containing the monodeprotonated ligand. Previously an X-ray crystal structure of $[Na(H_4L)H_2O]\cdot 2H_2O$ was carried out [4] as well as the determination of the structure of the anhydrous compound from X-ray powder data [9].

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2. Experimental

2.1. *Materials and methods*

Alendronic acid monohydrate was from a commercial pharmaceutical source. Lithium carbonate was of analytical reagent grade.

Electrospray mass spectra (ESMS) were recorded with a Bruker BioApec 47e FTMS with a 4.7 T superconducting magnet and fitted with an Analytica Electrospray Source. All samples were dissolved in water/methanol solution prior to analysis. Infrared (IR) spectra were recorded between 4000 and 650 cm^{-1} as Nujol mulls between NaCl plates using a Perkin Elmer 1600 FTIR instrument. The melting point was determined in a glass capillary and is uncalibrated. ^{1}H NMR, solution ^{31}P NMR, and ^{31}P solid-state NMR (MAS) spectra were recorded with a Bruker DPX400 spectrometer using the Bruker Topspin 2.1 program. Proton and phosphorus chemical shifts are in parts per million relative to tetramethylsilane or external 85% H_3PO_4, respectively, for solution experiments, and to external $(NH_4)_3PO_4$ for the solid-state experiments. Elemental analyses were obtained in duplicate and were performed by Campbell Microanalytical Laboratories, University of Otago, Dunedin, New Zealand. The powder X-ray diffraction (XRD) experiment was conducted using a Philips 1140 diffractometer with a Cu anode at $\lambda = 1.5418$ Å and a carbon monochromator on a sample thoroughly ground in an agate mortar prior to measurement. The weight loss experiment was performed on an accurately weighed sample that was heated to 180°C until constant weight was achieved.

2.2. *Synthesis of [Li(H$_4$L)(H$_2$O)$_2$] (1)*

Lithium carbonate, Li_2CO_3 (0.74 g, 10 mmol), and alendronic acid (5.34 g, 20 mmol) were added to water (200 mL), and after the evolution of CO_2 ceased, the reaction mixture was heated and stirred for *ca* 4 h. The crude white bulk precipitate was washed with copious amounts of hot water and dried at room temperature (Yield 5.06 g, 87%), m.p. 260–265°C. Anal. Calcd for $C_4H_{16}LiNO_9P_2$ (%): C 16.51, H 5.54, N 4.81. Found (%): C 16.63, H 5.66, N 4.69. IR (Nujol mull, cm^{-1}): 3533(vs, br), 3481(vs, br), 3418(vs, br), 3355(vs, br), 3299(vs, br), 1683(m), 1655(m), 1622(m), 1583(m), 1510(s), 1342(m), 1178(s), 1154(sh, s), 1074(s), 1051(s), 988(s), 921(s), 892(m), 854(m), 830(m), 747(m). IR of anhydrous Li alendronate (Nujol mull, cm^{-1}): 3518(m), 3287(s), 3175(s), 1735(m), 1643(m), 1519(s), 1327(m), 1312(m), 1267(m), 1170(s), 1082(s), 1021(s), 922(s), 879 (sh,m), 858(m), 827(m), 770(m). ^{1}H NMR (D_2O, ppm): δ 2.99 (m, 2H, CH_2N), 1.96 (m, 4H, CH_2CH_2). ^{31}P NMR ((D_2O, ppm): δ 18.2 (s). ^{31}P MAS NMR: δ 18.8 (br) and 15.8 (br) ppm. ^{31}P MAS NMR of alendronic acid hydrate: δ 15.8 (br) and 14.7 (br) ppm (Lit. [10] 16.6, 15.9 ppm, relative to bis(diisopropoxythiophosphoryl)disulfide). ESMS (only ^{7}Li ions listed) (+ve): m/z 85 [100%, $Li(CHP(OH)_2)^+$], 256 [7, $Li(H_5L)^+$], 262 [13, $Li_2(H_4L)^+$], 511 [3, $Li_2(H_5L)(H_4L)^+$], 517 [9, $Li_3(H_4L)_2^+$]; (−ve): 166 [23%, $(H_4L - H_3PO_3)^-$], 194 [10, $(H_4L - 3H_2O)^-$], 212 [9, $(H_4L - 2H_2O)^-$], 230 [11, $(H_4L - H_2O)^-$], 248 [100, H_4L^-], 503 [12, $Li(H_4L)_2^-$], 758 [4, $Li_2(H_4L)_3^-$]. Molar mass from pH titration with base: 293 g mol^{-1} (calculated value 291 g mol^{-1} for $C_4H_{16}LiNO_9P_2$). Weight loss: 12.7% (180°C, Calcd for loss of $2 \times H_2O = 12.4\%$).

2.3. *Crystal structure determination*

A crystalline sample of **1** deposited from the aqueous filtrate of the bulk product at room temperature. A single crystal was mounted on a glass fiber in viscous hydrocarbon oil. Data were collected on a Nonius KappaCCD diffractometer (equipped with monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) processed by using the DENZO [11] package (Bruker)) at 123 K. The structure was solved using direct methods, and observed reflections were used in least squares refinement on F^2, with anisotropic thermal parameters refined for non-hydrogen atoms. Hydrogens were constrained in calculated positions when bound to carbon, but all hydrogens bound to heteroatoms were located and refined. Structural solution and refinement were carried out using the SHELX suite of programs [12] with the graphical interface X-seed [13]. A summary of crystal data and structure refinement is given below. Selected bond lengths and angles are shown in table 1 and H-bonding bond lengths are shown in table 2.

Crystal data for **1**: $C_4H_{16}LiNO_9P_2$, $M = 291.06$, colorless block, 0.50 mm × 0.50 mm × 0.20 mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 8.9277(18)$, $b = 7.3943(15)$, $c = 16.828(3)$ Å, $\beta = 95.57(3)°$, $V = 1105.7(4)$ Å^3, $Z = 4$, $D_c = 1.748\ \mathrm{g\,cm^{-3}}$, $F_{000} = 608$, $2\theta_{max} = 55.0°$, 12,968 reflections collected, 2535 unique ($R_{int} = 0.0783$). Final goodness-of-fit $= 1.146$, $R_1 = 0.0345$, $wR_2 = 0.0942$, R indices based on 2280 reflections with $I > 2\sigma(I)$ (refinement on F^2), 194 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.431\ \mathrm{mm^{-1}}$.

3. Results and discussion

3.1. *Structure discussion*

Lithium alendronate was prepared by the reaction of lithium carbonate with alendronic acid. The bulk product was analyzed as $[Li(H_4L)(H_2O)_2]$, a composition corresponding with that of single crystals obtained from the filtrate after isolation of the bulk product.

Table 1. Selected bond lengths (Å) and angles (°) for **1**.

Bond lengths			
Li(1)–O(2)	1.920(3)	Li(1)–O(3)	1.884(3)
Li(1)–O(8)	1.916(3)	Li(1)–O(9)	1.917(3)
P(1)–O(3)	1.5002(11)	P(2)–O(2)	1.4932(12)
P(1)–O(4)	1.5805(13)	P(2)–O(6)	1.5195(12)
P(1)–O(5)	1.5129(12)	P(2)–O(7)	1.5773(12)
P(1)–C(1)	1.8515(17)	P(2)–C(1)	1.8490(16)
C(1)–O(1)	1.4542(17)		
Bond angles			
O(2)–Li(1)–O(3)	106.10(14)	O(8)–Li(1)–O(9)	103.30(14)
O(2)–Li(1)–O(8)	98.17(14)	O(3)–Li(1)–O(8)	130.84(17)
O(2)–Li(1)–O(9)	114.29(16)	O(3)–Li(1)–O(9)	104.45(15)
Li(1)–O(3)–P(1)	129.46(12)	Li(1)–O(2)–P(2)	126.14(11)
O(3)–P(1)–O(4)	107.87(7)	O(2)–P(2)–O(6)	115.43(7)
O(3)–P(1)–O(5)	115.98(7)	O(2)–P(2)–O(7)	110.19(7)
O(4)–P(1)–O(5)	110.23(7)	O(6)–P(2)–O(7)	109.66(7)
O(3)–P(1)–C(1)	110.23(7)	O(2)–P(2)–C(1)	110.03(7)
O(4)–P(1)–C(1)	103.47(7)	O(6)–P(2)–C(1)	107.39(7)
O(5)–P(1)–C(1)	108.33(7)	O(7)–P(2)–C(1)	103.43(7)

Table 2. Hydrogen bonds for **1** (Å and °).

D–H…A	d(D–H)	d(H…A)	d(D…A)	∠(DHA)
N1–H5…O2#1	0.93(3)	2.06(3)	2.900(2)	150(2)
N1–H7…O4#9	0.86(2)	2.56(3)	3.187(2)	130(2)
N1–H6…O5#7	0.89(3)	2.04(3)	2.866(2)	153(2)
N1–H7…O6#9	0.86(2)	2.35(2)	2.9487(19)	127(2)
N1–H5…O8#1	0.93(3)	2.60(3)	3.264(2)	129.3(19)
O1–H8…O4#10	0.75(3)	2.51(3)	3.1322(18)	142(3)
O1–H8…O6	0.75(3)	2.60(3)	2.9507(17)	111(2)
O4–H10…O6#3	0.65(3)	1.91(3)	2.5515(18)	172(4)
O7–H9…O5#4	0.89(3)	1.69(3)	2.5734(18)	168(3)
O8–H12…O1#6	0.82(3)	1.92(3)	2.7299(19)	169(3)
O8–H11…O7#5	0.77(3)	2.02(3)	2.7864(19)	168(2)
O9–H14…O3#8	0.83(3)	2.00(3)	2.8116(19)	164(3)
O9–H13…O6#2	0.85(3)	1.91(3)	2.7542(19)	176(2)

Symmetry transformations used to generate equivalent atoms: #1 $1-X, 1-Y, -Z$; #2 $2-X, 1-Y, -Z$; #3 $2-X, Y-1/2, 1/2-Z$; #4 $X, 1+Y, Z$; #5 $1-X, 1-Y, -Z$; #6 $X, 1/2-Y, Z-1/2$; #7 $1-X, 1/2+Y, 1/2-Z$; #8 $2-X, -Y, -Z$; #9 $X-1, Y, Z$; #10 $-X+2, Y+1/2, -Z+1/2$.

The complex crystallizes in the space group $P2_1/c$ with four of the formula units in the unit cell. **1** is a monomeric aquated lithium complex of alendronic acid in which one oxygen of each phosphonic acid group and two waters are coordinated to lithium, which has distorted tetrahedral stereochemistry (figure 1). The complex has a zwitterionic character with a terminal protonated amine group and two negatively charged phosphonates. The Li–O bond lengths (1.884(3)–1.920(3) Å, average 1.91 Å) are typical of those found in related compounds [4–6] and that expected using Shannon radii [14] (1.94 Å from the ionic radius of Li (0.59 Å) and O (1.35 Å)). Thus, Li–$O_{(\text{phosphonate})}$ bond lengths have been reported in the range of 1.9–2.1 Å for four-coordinate lithium [15–17]. The O–Li–O bond angles (98–130°) reflect the pronounced distortion from tetrahedral. The P–OH bond lengths (~1.58 Å) are greater than P–OLi (1.50 Å) or P–$O_{(\text{ter})}$ (1.52 Å) bond lengths. The last two evidently have 1.5 bond order and accommodate the negative charge balancing the Li^+ and NH_3^+ charges. The P–C, C–O, and C–C bond distances in **1** are also comparable with those in alendronic acid [2]. Extensive intermolecular hydrogen bonding occurs with all of the oxygens on the ligand component and hydrogens of other ligands (table 2) creating a supramolecular overall structure. Both P–OH and two NH_3^+ hydrogens are also involved in intermolecular H-bonding (figure 2). There is a mixture of strong intermolecular hydrogen bonding (D–A distances are <2.9 Å), where there are eight such contacts (figure 2) and weaker interactions (D–A distances 2.900–3.264(2) Å) where there are a further five (table 2). Overall, taking into consideration all hydrogen-bonding interactions, each complex is attached to 10 other molecules through H-bonding providing a highly complex 3-D array. Only one intramolecular H-bonding interaction is observed and utilizes the C–OH group. Possibly extensive H-bonding contributes to the high melting point of this compound (260–265°C).

The structure of the four-coordinate lithium complex differs entirely from those of aquated [4] and anhydrous [9] six-coordinate sodium alendronate in that the former is a mononuclear complex which polymerizes through H-bonding, whereas the sodium derivatives are polymeric through coordination interactions, both through phosphoryl oxygens and also through coordination of the C–OH group to a neighboring sodium [4, 9]. In the latter case H-bonding is superimposed on an already polymeric array.

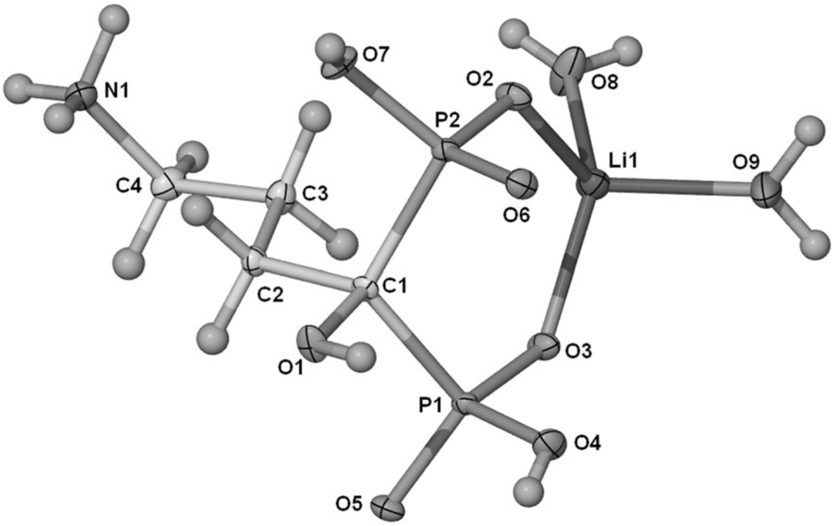

Figure 1. Molecular structure of [Li($C_4H_{12}NP_2O_7$)(H_2O)$_2$] (**1**). Ellipsoids are shown at 50% probability.

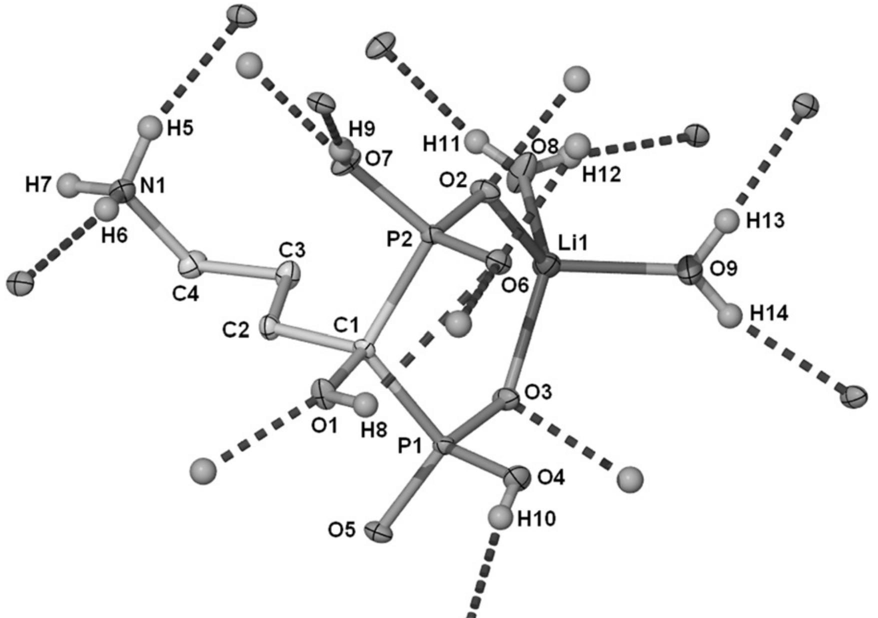

Figure 2. Molecular structure of **1** showing the extensive hydrogen bonding. Ellipsoids are shown at 50% probability.

Coordination of two waters to lithium in contrast to one with sodium is a key factor in the mononuclear nature of the present complex. Further, all Li–O bond lengths are similar, whereas the Na–O bond lengths cover a wide range, remarkably so in the anhydrous complex, owing to considerable variation in phosphoryl oxygen coordination in contrast to **1**. The terminal M–OH_2 bond lengths differ by 0.37 Å between the lithium and monoaquasodium complexes by comparison with 0.43 Å expected from ionic radii [14].

Powder XRD analysis of the bulk product of $[Li(H_4L)(H_2O)_2]$ confirmed that it was consistent with the crystalline material used in the single crystal X-ray structural determination. The diffraction pattern obtained from bulk analysis is essentially the same as that derived from the single crystal data (figure 3).

3.2. *IR, NMR, and mass spectra*

Multiple absorptions at 3600–3300 cm^{-1} ('Experimental' section) can be attributed to OH stretching of H_2O, P–OH, and C–OH groups as well as ν(NH) of the NH_3^+ group. Intense bands in the region 1200–900 cm^{-1} can be assigned to the stretching vibrations of the tetrahedral C–PO_3 groups [18, 19]. A bulk sample of $[Li(H_4L)(H_2O)_2]$ was heated to 180°C, where it lost 12.7% mass that corresponds well to the loss of two molecules of H_2O (12.4%). After drying, intense broad absorptions were lost from the IR spectrum between 3500 and 3300 cm^{-1} and did not reappear after exposure to moist atmosphere, implying anhydrous $[Li(H_4L)]$ does not readily reabsorb water.

The ^1H NMR spectrum of **1** is similar to that for the ligand [20] with only one $(CH_2NH_3^+)$ of the three different methylene groups able to be differentiated. The ^{31}P NMR spectrum in solution has only one resonance (18.2 ppm) which is again similar to the behavior of alendronic acid [20]. Two resonances in the solid state ^{31}P NMR spectrum (18.8 and 15.8 ppm) may reflect the two phosphorus environments (see e.g., differences in Li–O bond lengths (table 1)), but a more likely origin is the prochiral

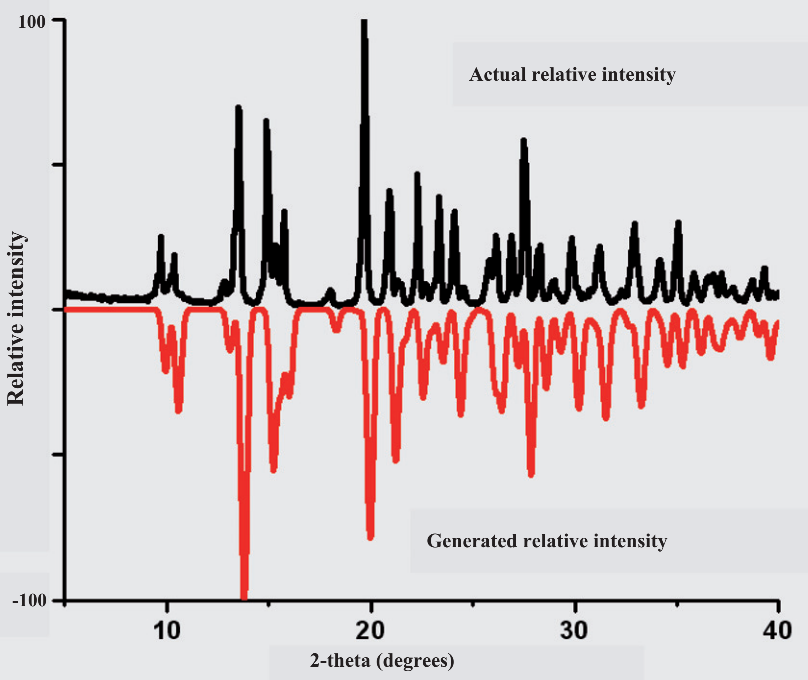

Figure 3. Powder XRD pattern of a bulk sample of $[Li(C_4H_{12}NP_2O_7)(H_2O)_2]$ (**1**) (top) compared with the generated diffraction pattern derived from single crystal data (bottom).

$C(PO_3)_2$ group combined with lack of rotation in the solid state. Two peaks are also found at 15.8 and 14.7 ppm for solid alendronic acid and can be similarly explained.

A number of lithium containing cations were identified in the +ve ESI spectrum of **1**, including the molecular ion $Li(H_5L)^+$ at 256 *m*/*z* but also lower intensity dilithium and trilithium species. In addition the –ve ESI spectrum indicates, besides the intense H_4L^- species, low intensity $Li(H_4L)_2^-$ and $Li_2(H_4L)_3^-$ ions, pointing to complex equilibria in solution. Given the monomeric nature of the central complex, it may be that H-bonding association, so prevalent in the solid, influences solution behavior.

Supplementary metarial

Crystallographic data (excluding structure factors) for the structure reported in this article and associated ESI have been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC 787984. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 (0) 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

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